Docket No.: 20555/1203301-US3
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Daniel G. Chain

Application No.: 10/084,380 | Confirmation No.: 3496

Filed: February 28, 2002 | Art Unit: 1649

For: **SPECIFIC ANTIBODIES TO AMYLOID BETA PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHODS OF USE THEREOF** | Examiner: K. A. Ballard

**DECLARATION OF KENNETH L. ROCK UNDER 37 C.F.R. §1.132**

MS RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Kenneth L. Rock declares and states as follows:

1. I am a citizen of the United States and am more than twenty-one years of age.

2. I am Professor and Chairman of the Department of Pathology at the University of Massachusetts Medical Center in Worcester, Massachusetts, and have held this position since 1997. I am a physician Board Certified in pathology and have conducted research in the field of immunology since the late 1970s. Specifically, I have studied T-cell, B-cell, and antibody responses, including the mechanisms by which antibody responses are generated. I have also conducted research on developing therapeutic monoclonal antibodies and using such antibodies to treat disease. I have in particular performed investigations using monoclonal antibodies *in vivo* to delete subsets of T-cell and NK cells, bind cell surface receptors to inhibit or stimulate immune responses and treat cancers, e.g., lymphomas, lung carcinomas and melanomas. I am familiar with Alzheimer's Disease through my medical training and work as a pathologist.

3. In 1994 I co-founded Corixa Corp., to develop immunotherapies to treat cancers and infectious disease. A major focus the company was the use of therapeutic antibodies to treat such conditions. Starting in 1994 and continuing through 2005 I consulted with Corixa on their antibody projects, including developing an antibody against cell surface gangliosides that was discovered in my laboratory, for treatment of human cancers. I have also consulted for other biotechnology and pharmaceutical companies on the use of antibodies as therapeutic agents, and I have lectured on the use of antibodies as therapeutic agents in courses given to graduate students, medical students, and at pharmaceutical companies.

4. I am a co-inventor of three U.S. patents, including U.S. Patent No. 6,693,176, entitled, "Antitumor antibodies, proteins and uses thereof." This application discloses a monoclonal antibody that binds specifically to a protein that is expressed on tumors, but is not expressed on normal adult hemopoietic cells, and methods of using this antibody to treat human cancers.

5. A copy of my curriculum vitae is attached as Exhibit A.

6. I am not a co-inventor of the subject patent application and have no financial or business interest in Intellect Neurosciences, Inc., a company that I understand has rights in this patent application.

7. I have been asked for my opinion on whether the specification of provisional application 60/041,850, filed April 9, 1997, describes methods for inhibiting accumulation or neurotoxicity of Aβ by contacting soluble Aβ in the cerebrospinal fluid of a patient suffering from Alzheimer's Disease with a free-end specific antibody to Aβ with sufficient detail, such that it would have conveyed to one of ordinary skill in the art at that time that the inventors had possession of the methods. This opinion is based only on the disclosure of the provisional application, as it would have been understood by one of ordinary skill in the field of the application as of April 9, 1997, the filing date of the provisional application.

8. In forming my opinion, I considered the provisional application, the subject patent application (serial no. 10/084,380), the parent of the subject patent, international application PCT/US98/06900, filed April 8, 1998 and published as WO 98/44955, the Office Action for the

subject application that is dated September 13, 2006, the pending claims that were filed on June 30, 2006, and certain of the patent and non-patent literature cited in the provisional application.

9. Based on my review of the provisional application and my experience in the field of using antibodies to treat human disease, I conclude that:

(i) The provisional application describes all of the features set forth in the claimed methods for inhibiting accumulation or neurotoxicity of Aβ by contacting soluble Aβ in the cerebrospinal fluid of a patient suffering from Alzheimer's Disease with a free-end specific antibody to Aβ;

(ii) No later than April 9, 1997, a person of ordinary skill upon reading the provisional application would have concluded that the inventor was in possession of methods for inhibiting accumulation or neurotoxicity of Aβ by contacting soluble Aβ in the cerebrospinal fluid of a patient suffering from Alzheimer's Disease with an antibody; and

(iii) A person of ordinary skill would have concluded that the method for contacting soluble Aβ in the cerebrospinal fluid of a patient suffering from Alzheimer's Disease with an antibody was not limited to gene therapy, i.e., gene therapy was only one of a number of approaches that could be used to contact soluble Aβ in the cerebrospinal fluid of a patient suffering from Alzheimer's Disease an antibody.

10. My first reason for arriving at these conclusions is that the provisional application clearly conveys that the inventor had possession of a free-end specific antibody per se, which could be administered to a patient through any means. Thus, Fig. 3 and 4 of the provisional application disclose antibodies and antibody derivatives generally. The provisional application at page 13, lines 13-16 and page 14, line 27 through page 15, line 5 discusses "antisenilin" antibodies, standing alone. Further discussion of antibodies and antibody derivatives is found in the provisional application at page 16, line 20 through page 17, line 9 (methods of producing hybridoma and characterizing free-end specific antibodies), page 19, lines 10–15 (evaluation of Kd and efficacy of Aβ end-specific antibodies in blocking Aβ aggregation and Aβ-induced cytotoxicity), page 30-36 (methods for making and characterizing antibodies), and pages 43-46 (testing antibody for

therapeutic effects), e.g., page 43, lines 4-9 (using antibody to contact to contact and neutralize amyloid β-peptide). Thus, the provisional application discloses free-end specific antibodies per se and their usefulness in counteracting toxic effects of Aβ. Finally, claim 14 of the provisional application reads, "Monoclonal antibody end-specific for the N-terminus of an amyloid β-peptide." In my opinion, these passages demonstrate that the inventors contemplated production of antisenilins per se, i.e., outside of the body.

11. The provisional application further sets out that extracellular neuritic plaques are the pathogenic lesion in Alzheimer's Disease (page 1, lines 26-28, neuritic plaque strongly correlated with reactive and degenerative processes; and page 2, lines 2-3, principal component of neuritic plaque Aβ1-42), that secretion of soluble Aβ into the CSF is amyloidygenic (page 3, lines 10-12, Aβ present in CSF in vivo) and that "one therapeutic approach is to inhibit or retard Aβ aggregation" (page 6, lines 8-10). Thus, the specification of the provisional application clearly sets out that treatment of Alzheimer's disease requires treating extracellular Aβ peptides before they have a chance to assemble into neuritic plaques and that in order to be therapeutic antisenilin must have access to the CSF.

12. Moreover, the provisional application repeatedly discloses that the purpose of expressing a free end specific antibody to Aβ is to provide the antibody to the CSF, where it will contact soluble Aβ, preventing accumulation of Aβ into plaques. I understand clearly from this that the actual therapeutic agent is not a gene but, rather, is the antisenilin protein, more specifically antisenilin in the CSF. Thus, the provisional application sets forth (underling added):

> These ectopically expressed recombinant antibody molecules, which are end-specific for the N-terminus or C-terminus of amyloid-β peptides, prevent the accumulation of amyloid-β peptides in the extracellular space and the aggregation of such peptides into amyloid deposits in the brain.

Page 9, line 21-26.

> Another object of the invention is to provide a method whereby cells of the nervous system are conferred with the ability to ectopically express recombinant antibody

molecules in the brain, which molecules are end-specific for the N-terminus or C-terminus of amyloid β peptides, to prevent the accumulation of amyloid-β peptides in the cerebrospinal fluid and the aggregation of such peptides into amyloid deposits in the brain.

Page 10, lines 14-21.

Figure 1 also schematically shows that the stable expression and secretion of ectopic Aβ-end-specific antibodies in the CNS inhibits (1) the accumulation of Aβ peptides and (2) neurotoxic consequences of amyloid deposition without affecting the biological functions of the soluble β-amyloid precursor protein.

Page 11, lines 20-25.

By "antisenilin" is meant a molecule which binds specifically to a terminus/end of an Aβ peptide to prevent the accumulation of amyloid-β peptides in the extracellular space and the aggregation into senile amyloid plaques or deposits.

Page 13, lines 12-16.

The secretion of antisenilins into the cerebrospinal fluid, where soluble Aβ peptides are present, promotes the formation of soluble antisenilin-Aβ complexes. These soluble complexes are cleared from the central nervous system... In this manner, soluble Aβ peptides are prevented from accumulating in the extracellular space to form amyloid deposits and/or induce neurotoxicity (Fig. 1).

Page 13, line 21 through page 14, line 3.

The secreted antisenilins then form a soluble complex with Aβ peptide to which they are end-specific in the cerebrospinal fluid. These soluble antisenilin-Aβ peptide complexes prevent the aggregation of Aβ peptides into amyloid deposits and prevent Aβ-induced neurotoxicity by clearing Aβ peptides from the central nervous system through drainage of the cerebrospinal fluid into the general blood circulation where they will be eliminated by protease digestion. Accordingly, the

> accumulation of newly-secreted soluble Aβ peptides responsible for amyloid deposition and Aβ-induced neurotoxicity is prevented.

Page 28, lines 12-22.

The provisional application further sets forth more generally:

> [T]he present method is directed to preventing the accumulation of Aβ peptides in the extracellular milieu of affected neurons as the focal point of this heterogeneous pathological cascade.

Page 10, lines 3-6.

I was working in the field of antibodies in 1997, i.e., at the time the provisional application was filed. Had I (or one of the post-doctoral students working with me) read the provisional application at that time, I (and the post-doctoral student in my lab) would have recognized immediately that the inventor was in possession of a method of inhibiting the accumulation of Aβ or inhibiting the neurotoxicity of Aβ by contacting soluble Aβ in the cerebrospinal fluid of a patient suffering from Alzheimer's Disease with a free-end specific antibody to Aβ.

13. Furthermore, the provisional application discloses treating Alzheimer's disease generally, without reference to gene therapy. Thus, the provisional application states among the objects of the invention are to "overcome the deficiencies in the prior art by providing a novel method for preventing or inhibiting the progression of Alzheimer's disease" (page 10, lines 11-13), "provide a method for preventing or inhibiting the progression of Alzheimer's Disease by also inhibiting the interaction of amyloid-β peptides mediating amyloid-β induced neurotoxicity and inhibiting the amyloid-β induced complement activation and cytokine release involved in the inflammatory process associated with Alzheimer's Disease" (page 10, line 22 - page 11, line 2), and "provide a pharmaceutical composition for preventing or inhibiting the progression of Alzheimer's Disease (page 11, lines 12-14). Based on these statements and the balance of the specification, it is my opinion that on the filing date of the provisional application, the inventor generally had possession of compositions for treating Alzheimer's disease and methods of using such compositions to treat Alzheimer's disease, without reference to gene therapy.

14. I find nothing in the provisional application that indicates recombinant expression of antibodies specific for a free-end of Aβ is the only way of providing such antibodies to the CSF of Alzheimer's patients. The provisional application includes a separate section that begins on page 43, entitled, "ANIMAL MODELS TO ESTABLISH THE THERAPEUTIC POTENTIAL OF THE αβ ANTIBODIES AS ANTISENILINS." This section sets out to measure the "antisenilin function" of viral vectors expressing anti-Aβ end specific antibodies (page 43, lines 21-23) and sets as an end-point the clearance of Aβ and Aβ-antisenilin complexes from CSF (page 45). As someone who was working in the field at the time (and supervising scientists of ordinary skill in the art in the field of the invention), it is my opinion that in 1997 this section would clearly have conveyed to one of ordinary skill in the art that the therapeutic potential lies in the activity and effect of the end-specific antibodies, not the means by which such antibodies are administered.

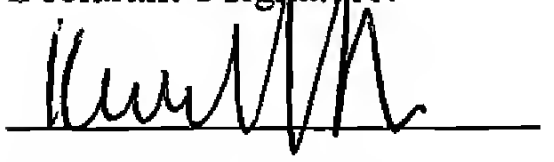
15. Moreover, it is my opinion that as of the filing date of the provisional application, upon reading the specification, one of ordinary skill in the art would have immediately appreciated that treatment of Alzheimer's disease by contacting soluble Aβ in the CSF with a free-end specific antibody could be effected by directly administering such antibodies to a patient. The references cited in the application provide evidence that direct administration of antibodies was well known to those of ordinary skill in the art. Thus, Konig, WO 96/25345 (attached as Exhibit B and cited in the provisional application at page 7, line 16) at page 7, lines 20-25 discloses "methods for the prevention of aggregation of βA4 peptide by administering monoclonal antibody of the instant invention." Cabilly, U. S. Patent No. 4,816,567 (attached as Exhibit C and cited in the provisional application at page 15, line 13) at col. 2, lines 27-35 discloses that "antibodies can be directly injected into subjects suffering from an attack by a substance or organism containing the antigen in question to combat this attack" and that "whole body diagnosis and treatment is made possible because injected antibodies are directed to specific target disease tissues." Huston, et al., U.S. Patent No. 5,091,513 (attached as Exhibit D and cited in the provisional application at page 16, line 5) at col. 8, line 9 discloses "clinical administration" of chimeric antibodies. Piccioli, et al., Proc. Natl. Acad. Sci. USA 88:5611 (1991) (attached as Exhibit E and cited in the provisional application at page 9, line 3 with full citation at page 52) at page 5614, col. 1 under section labeled "Discussion" sets out explicitly that gene-transfer techniques are an "extension" of antibody

injections. These references demonstrate to me that direct administration of therapeutic antibodies was well know in the art. Upon reading the provisional application, I would have immediately appreciated that treatment of Alzheimer's disease by contacting soluble Aβ in the CSF with a free-end specific antibody could be effected by directly administering such antibodies to a patient.

16. Thus, for the reasons set forth in paragraphs 10-15, it is my opinion that on April 9, 1997 (the filing date of the provisional application), the inventor had invented the methods of inhibiting accumulation or neurotoxicity of Aβ by contacting soluble Aβ in the CSF of a patient suffering from Alzheimer's Disease with a free-end specific antibody to Aβ that are called for in the claims that are pending in the present application and, further, had described them in the provisional application in such a manner as to convey to one of ordinary skill in the art that the inventor had possession of such methods.

17. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Declarant's signature:



8-17-07

Kenneth L. Rock, M.D. Date